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| 10/518,427 | 09/30/2005 | Andrew David Miller | CU-4022 RJS | 6762 |

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| EXAMINER | |
|---|---|
| LAO, MARIALOUISA | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/518,427 | MILLER ET AL. | |
| | Examiner | Art Unit | |
| | Louisa Lao | 1621 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12/5/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *61-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-119* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/28/06, 12/20/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Arguments*

1. Applicant's arguments, filed 12/5/07, have been fully considered, as follows:

a) with respect to the rejection(s) of claim(s) 108-112 and 115 under 35 U.S.C. 112, first paragraph and are not persuasive. The rejection of claims 108-112 and 115 is maintained.

b) with respect to co-pending applications

b1) double patenting rejection of claim(s) 61-119 on the grounds of nonstatutory obviousness-type double patenting over the claims 1,9,13,20-23,32,33,39-44 and 48 of copending Application No. 10/484855 (US2004/0219202); this rejection is maintained.

b2) provisional rejection(s) under 102(e)/103 claims 61-119 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 27 and 37-41 of copending Application No. 10/550129 (US2007/009608) and claims 143 and 154 of copending Application No. 10/550033 (US2007/0015795), respectively have been obviated by Applicants' responses as to dates of priority. Therefore, the rejections have been withdrawn.

c) with respect to rejection under 102(f)/103 or 102(g)/103 of claims 61-119 over US`202 have been obviated by Applicants' responses as to earlier date of priority. Therefore, the rejection has been withdrawn.

However, upon further consideration, a new ground(s) of rejection is made, see below.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. The rejection of claims 108-112 and 115 is maintained under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

4. Claims 108-112 and 115 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of lowering concentration of cholesterol and triglycerides in the blood of mammals comprising administering to said subject an effective amount of a compound of Formula I, as recited, does not reasonably provide enablement for a) method for *inhibiting* the oxidative modification of low density lipoprotein, b) a method for *producing weight loss or a reduction* of the fat mass in a human or non-human animal in need thereof, c) a method for the *modification of the fat distribution* and content of animals, d) a method of *inhibiting or preventing* the growth of tumors, e) a method for the treatment or *inhibition* of primary and secondary metastatic neoplasms, f) a method for the prevention or treatment of proliferative skin disorders, g) a method for the *inhibition* of proliferation or induction of differentiation of keratinocytes, h) a method for the *prevention* or treatment of inflammatory disorders, i) a method for enhancing the endogenous production of interleukin-10 in mammalian cells or tissues, j) a method for suppression of the endogenous production of interleukin-2, k) a method for the inhibition of proliferation of stimulated peripheral mononuclear cells. The specification does not enable the person skilled in the art, to make the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized as a) the quantity of experimentation necessary, b)

the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in the art, g) the predictability or unpredictability of the art, and, h) the breadth of the claims.

5. In the present case, the important factors leading to a conclusion of undue experimentation are the absence of any working example of the aforementioned methods (a-k), the lack of predictability in the art, the amount of direction and guidance provided and the broad scope of the claim.

*a) the nature of the invention and the e) the state of the prior art.* Methods using phospholipid compounds of similar structure as recited in Formula (I) are known, see Jamila et al. (US2004192908, US`908 *in IDS*).

*b) the breadth of the claim.* Claims 108-112 and 115 recite methods (a-k), as discussed *supra* comprising administering to said subject an effective amount of a compound of Formula I. This is broad.

*c)the amount of direction and guidance provided.* The specification on page 65-78 recites the experiments using Wistar rats and the evaluations performed, including *inter alia* lipid lowering effects, fatty acid oxidation, activity of mitochondrian enzymes, carnitine palmitoyltransferase-II.

*d) the presence or absence of working examples.* There are no working examples of methods (a-k) for inhibition or prevention of disorders, illustratively of primary and secondary metastatic neoplasms, proliferative skin disorders. The various examples presented are found deficient to encompass the plurality of disorders and the population of humans and animals with said disorders.

*e) the amount of experimentation needed.* Since the compounds of Formula I are replete with substituents effectuating to different structures with invariable distinct characteristics, the quantity of experiments corresponding to the method of treatment for the recited disorders thereto, would likewise be numerous.

*f) the relative skill of those in the art.* The skilled artisans are synthetic organic chemists and clinical pharmacists with graduate degrees and potentially with many years of research and industrial experience.

*g) the predictability or unpredictability of the art.* The state of the art of method of treatment is unpredictable, since this art is largely empirical, which requires fulfilling a rationale for the optimization of absorption, distribution, metabolism, and excretion of a drug. Determining whether a compound meets the attributes of a useful prodrug entails substantial clinical testing with laborious experimentation. See Goodman & Gilman's *The Pharmacological Basis of Therapeutics".* 10th ed. NY McGraw Hill 2001 p3.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed.Cir.1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

- Applicants argue that the utility of the invention is disclosed, citing the specification and international patent applications therein. However, Applicants' cited references are Applicants' own work. Albeit, US7230029 *equivalent to cited WO02/26218*, a published patent is drawn to proliferation and/or differentiation of keratinocytes, it does not encompass the breadth of the instant claims. Further, each case is examined on its merits.
- Applicants affirmed that the number of compounds encompassed by the claims is large, while alleging that complex experimentation is not undue and is expected. However, *arguendo* one of ordinary skill in the art at the time of Applicants' invention would engage in ertswhile complex experimentation, would still have to determine permutations of potential compounds *before* engaging in said complex experiments and engage in vast experimentation to determine the modes of administration, levels of dosage for equally numerous compounds of formula (I).

- Hence, Applicants' arguments *in toto* are not persuasive and the rejection stands.

6. Claims 61-100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of the formula (I), when Y=S, X= $C_6$-$C_{24}$ alkyl or X= $C_6$-$C_{24}$ alkenyl containing one or more double bonds and optionally one or more triple bonds, Z=$CH_2$, when p=2 and PHG=formula (II) and formula (III) , it does not reasonably provide enablement for the claimed compound of formula (I) where Y= other than S; Z=other than $CH_2$ and X=other than those stated previously and PHG=other than those stated previously and p=1 or 3, as suggested by the breadth of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims. The factors to be considered [in making an enablement rejection] have been summarized as a) the nature of the invention, b) the breadth of the claims, c) the state of the prior art, d)the relative skill of those in the art, e) the predictability or unpredictability of the art, f) the amount of direction or guidance presented, g) the presence or absence of working examples, and h) the quantity of experimentation necessary.

*a) the nature of the invention*: the instant claims are drawn to a lipid compound of formula (I), with substituents as therein recited.

b) *the breadth of the claims:* Independent claim 1 is extremely broad in that it recites a broad array of compounds. While the dependent claims, thereto recite permutations of the substituents therein recited that equally encompass an even broader array of compounds.

*c&e) state and predictability of the art.* The claimed compounds are not novel. The structures of said lipid are taught by Ruoxin et al. *Sulfur-substituted Phosphatidylethanolamines.* J.Org.Chem. 1993, 58, 1952-1954.

*d)the relative skill of those in the art:* the skill is high.

*e&f)amount of guidance present and working examples.* The instant disclosure provides guidance for the process of making TTA-18, -19 and -20. There is no guidance to compounds other than the compounds of the formula (I), when Y=S, X= $C_6$-$C_{24}$ alkyl or X= $C_6$-$C_{24}$ alkenyl containing one or more double bonds and optionally one or more triple bonds, Z=$CH_2$, when p=2 and PHG=formula (II) and formula (III).

*g) quantity of experimentation needed.* The quantity of experimentation required of a person having ordinary skill in the art could potentially be infinite without further guidance. Without further guidance, a person of ordinary skill may have to experiment with the activity and selectivity of a vast array of permutations of the instant compound of formula (I) to determine which of these compounds can be effective by way of the functionality of the compound described in the instant claim(s). All these elements taken into consideration make the experimentation unduly burdensome.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed.Cir.1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

7. Claims 101-119 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of lowering concentration of cholesterol and triglycerides in the blood of mammals comprising administering to said subject an effective amount of a compound of Formula I, where said compound of formula (I) are the compounds

when Y=S, X= $C_6$-$C_{24}$ alkyl or X= $C_6$-$C_{24}$ alkenyl containing one or more double bonds and optionally one or more triple bonds, Z=$CH_2$, when p=2 and PHG=formula (II) and formula (III) , it does not reasonably provide enablement for method of using the claimed compound of formula (I) where Y= other than S; Z=other than $CH_2$ and X=other than those stated previously and PHG=other than those stated previously and p=1 or 3, for a) method for *inhibiting* the oxidative modification of low density lipoprotein, b) a method for *producing weight loss or a reduction* of the fat mass in a human or non-human animal in need thereof, c) a method for the *modification of the fat distribution* and content of animals, d) a method of *inhibiting or preventing* the growth of tumors, e) a method for the treatment or *inhibition* of primary and secondary metastatic neoplasms, f) a method for the prevention or treatment of proliferative skin disorders, g) a method for the *inhibition* of proliferation or induction of differentiation of keratinocytes, h) a method for the *prevention* or treatment of inflammatory disorders, i) a method for enhancing the endogenous production of interleukin-10 in mammalian cells or tissues, j) a method for suppression of the endogenous production of interleukin-2, k) a method for the inhibition of proliferation of stimulated peripheral mononuclear cells. The specification does not enable the person skilled in the art, to make the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in the art, g) the predictability or unpredictability of the art, and, h) the breadth of the claims.

8. In the present case, the important factors leading to a conclusion of undue experimentation are the absence of any working example of the aforementioned methods (a-k), the lack of predictability in the art, the amount of direction and guidance provided and the broad scope of the claim.

*a) the nature of the invention and the e) the state of the prior art.* Methods using phospholipid compounds of similar structure as recited in Formula (I) are known, see Jamila et al. (US2004192908, US`908 *in IDS*).

*b) the breadth of the claim.* Claims 101-119 recite methods (a-k), as discussed *supra* comprising administering to said subject an effective amount of a compound of Formula I. These are broad because the compounds of formula (I) with the substituents as recited are vast, and equally the permutations thereto are large, as well and in the same token, the methods would be large, too.

*c)the amount of direction and guidance provided.* The specification on page 65-78 recites the experiments using Wistar rats and the evaluations performed, including *inter alia* lipid lowering effects, fatty acid oxidation, activity of mitochondrian enzymes, carnitine palmitoyltransferase-II, geared towards some compounds of formula (I).

*d) the presence or absence of working examples.* There are no working examples of methods (a-k) for *inhibition* or prevention of disorders, illustratively of primary and secondary metastatic neoplasms, proliferative skin disorders. The various examples presented are found deficient to encompass the plurality of disorders and the population of humans and animals with said disorders. There is no guidance to the method of use of the claimed compound of formula (I) where Y= other than S; Z=other than $CH_2$ and X=other than those stated previously and PHG=other than those stated previously and p=1 or 3.

*e) the amount of experimentation needed.* Since the compounds of Formula I are replete with substituents effectuating to different structures with invariable distinct characteristics, the quantity of experiments corresponding to the method of treatment for the recited disorders thereto, would likewise be numerous.

*f) the relative skill of those in the art.* The skill is high.

*g) the predictability or unpredictability of the art.* The state of the art of method of treatment is unpredictable, since this art is largely empirical, which requires fulfilling a rationale for the optimization of absorption, distribution, metabolism, and excretion of a drug. Determining whether a compound meets the attributes of a useful prodrug entails substantial clinical testing with laborious experimentation. See Goodman & Gilman's *The Pharmacological Basis of Therapeutics".* 10th ed. NY McGraw Hill 2001 p3.(submitted in Office Action mailed 7/26/07).

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed.Cir.1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 61-100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 61 defines the substituent PHG as -W-Linker-HG, however, there is no definition of this variable.

***Provisional Obviousness Double Patenting Rejection***

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. The provisional rejection of claims 61-119 is maintained on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over *claims 1,9,13,20-23,32,33,39-44 and 48 of copending Application No. 10/484855 (US2004/0219202).* Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant lipid compound of formula (I) is the same as the copending application's lipid compound when the instant substituents of formula (I) match. Illustratively, when X=$C_6$-$C_{24}$ containing one or more double bonds; Y= O or $CH_2$, Z=$C_{1-10}$ alkyl group; PHG=polar head group and the use of said lipid compound for the treatment of a disorder.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Claim Rejections - 35 USC § 102***

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 61-64, 67, 84 and 86 are rejected under 35 U.S.C. 102(b) as being anticipated by Ruoxin et al. *Sulfur-substituted Phosphatidylethanolamines.* J.Org.Chem. 1993, 58, 1952-1954.

15. The instant claims are drawn to a lipid compound of formula (I) $(XYZ\text{-}C{=}O)_p$-PHG with substituents as defined therein, a combination of a liposome and a compound of formula (I), a method for the production of a lipid compound of formula (I), a cosmetic formulation comprising a lipid compound of formula (I), a method of making the compound of formula (I), a pharmaceutical composition comprising a compound of formula (I) and a method of treating a plurality of disorders selected from, *inter alia,* Syndrome X, obesity, comprising administering to a subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

16. Ruoxin et al. teach sulfur-substituted phosphatidylethanolamines of the formula 11 (see page1952) and the synthesis routes to make the diacylglycerol-sulfur-containing phosphatidylethanolamines (pp1952-1954).

17. Ruoxin et al. anticipates the instant claims when X= $C_9$ alkyl, Y=S, Z=$C_6$ alkyl, p=2 and PHG = formula III.

18. No claims are allowed.

***Conclusion***

19. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Delfino, Jose M. et al. Tetrahedron Letters (1987), 28(21), 2327-30 and Tetrahedron Letters (1987), 28(21), 2323-6, Silvius et al. Biochemistry (1987), 26(14), 4279-87.

## *Correspondence*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MLouisa Lao whose telephone number is 571-272-9930. The examiner can normally be reached from 8:00am to 8:00pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Porfirio Nazario-Gonzalez/
Primary Examiner, Art Unit 1621

`mll02122008
MLouisa Lao
Examiner
Art Unit 1621

*for* YVONNE EYLER
SUPERVISORY PATENT EXAMINER
TC1600 GAU 1621